ORIGINAL ARTICLE

B-Cell Subsets in Patients With Transient Hypogammaglobulinemia of Infancy, Partial IgA Deficiency, and Selective IgM Deficiency

FE Çipe,[1] F Doğu,[1] D Güloğlu,[1] C Aytekin,[1] M Polat,[1] Z Bıyıkli,[2] A Ikincioğulları[1]

[1]Department of Pediatric Immunology-Allergy, Ankara University School of Medicine, Ankara, Turkey
[2]Department of Biostatistics, Ankara University School of Medicine, Ankara, Turkey

Abstract

Background: The pathogenesis of some primary humoral immunodeficiencies, such as transient hypogammaglobulinemia of infancy (THI) and immunoglobulin (Ig) A deficiency, remains unknown and can render diagnosis problematic.
Objective: In the present study, we used flow cytometry to analyze peripheral blood B-cell subsets in patients with THI and unclassified hypogammaglobulinemia (UCH), partial IgA deficiency, and selective IgM deficiency.
Methods: The study population comprised 41 patients with hypogammaglobulinemia (THI, 18; UCH, 23), 16 patients with partial IgA deficiency, and 16 patients with selective IgM deficiency who were admitted to Ankara University Department of Pediatric Immunology-Allergy between January 2010 and April 2011, as well as 29 healthy controls. B-cell subsets were examined according to the EUROclass classification.
Results: Age at diagnosis in the hypogammaglobulinemia group ranged between 14 months and 13 years (median, 26 months). Naive B-cell percentages were significantly higher and activated B-cell values lower in the THI patients than in the UCH patients and age-matched healthy controls. Nonswitched ($IgM^+CD27^+IgD^+$) memory B-cell values were found to be significantly lower in patients with selective IgM deficiency than in healthy controls. No significant differences in B-cell subsets were found in patients with partial IgA deficiency.
Conclusions: Previous reports show that reduced class-switched memory B cell values are associated with CVID, THI, and selective IgA deficiency. Our findings did not support these reports. Furthermore, we observed that naive B cell values were higher in patients with THI. A maturation defect could play a role in the pathogenesis of THI.

Key words: Hypogammaglobulinemia. IgA deficiency. IgM deficiency. Memory B cell.

Resumen

Antecedentes: La patogénesis de algunas inmunodeficiencias primarias tales como la hipogammaglobulinemia transitoria de la infancia (THI), el déficit de IgA permanece desconocida y a veces es motivo de un problema en su diagnóstico.
Objetivos: El motivo de este estudio fue analizar mediante citometría de flujo, las subclases de células B en sangre periférica en pacientes con THI junto con hipogammaglobulinemias no clasificadas (UCH) , deficiencias parciales de IgA y deficiencias selectivas de IgM .
Métodos: Se incluyeron 41 pacientes con hipogammaglobulinemia (THI:18 y UCH:23 pacientes), 16 con déficit parcial de IgA, 16 con deficiencia selectiva de IgM y 29 controles sanos admitidos en Ankara University, Departamento de Pediatría e Inmunología -Alergia. Se examinaron las subclases de células B de acuerdo con la clasificación Euroclass. Los pacientes fueron vistos entre enero de 2010 y abril de 2011.
Resultados: En el grupo de hipogammaglobulinemia, la edad en el diagnóstico se encontraba en un rango entre 14 meses y 13 años (Med: 26 meses). Las células B naive se encontraban significativamente elevadas y las células B activadas disminuídas en el grupo THI respecto al grupo UCH y los controles sanos. Las células B memoria (IgM+ CD27+ IgD+) se encontraban significativamente disminuídas en pacientes con diagnóstico de déficit selectivo de IgM. En la deficiencia parcial de IgA no se encontraron diferencias en las subclases de células B.
Conclusiones: Nuestros resultados no confirman resultados previos de una reducción de células B memoria relacionada con CVID, THI y selectiva deficiencia de IgA. Encontramos un aumento de células B naive en pacientes con hipogammaglobulinemia transitoria, sugiriendo un defecto de maduración que puede jugar un papel en la patogénesis de esta enfermedad.

Palabras clave: Hipogammaglobulinemia. Deficiencia de IgE. Deficiencia de IgM. Células B memoria.

Introduction

Hypogammaglobulinemia is defined as a decrease of 2SD in the levels of at least 1 of the immunoglobulin (Ig) isotypes compared to mean values for age. IgG levels reach their lowest values at 3-6 months of age (normal-physiologic hypogammaglobulinemia). Hypogammaglobulinemia persisting beyond 6 months of age is referred to as transient hypogammaglobulinemia of infancy (THI) [1,2].

THI is characterized by prolonged hypogammaglobulinemia that resolves spontaneously by 2-3 years of age, although improvement may not be seen until 5-6 years in some patients [2-4]. Because of this conflict in terminology, patients with persistent hypogammaglobulinemia after 3 years of age are considered to have "unclassified hypogammaglobulinemia" (UCH) [4]. Although the pathogenesis of THI remains unclear, the disease is thought to be due to a maturation defect of Ig synthesis [2,4].

Selective IgA deficiency (sIgAD) is the most prevalent primary humoral immunodeficiency and is defined as IgA levels <7 mg/dL in children >4 years of age. A 2SD decrease in IgA level is termed partial IgAD [1]. The various pathogenic mechanisms postulated for sIgAD include IgA-specific suppressor T-cell activity, inadequate helper T-cell function, an intrinsic B-cell defect, and decreased expression of CD49 on monocytes [5,6]. sIgAD is considered to be genetically associated with common variable immunodeficiency (CVID), since CVID can develop from sIgAD [7,8].

Selective IgM deficiency (sIgMD) is a rare dysgammaglobulinemia characterized by a decreased serum IgM level <2SD or <20 mg/dL with normal levels of the other Ig isotypes. For the diagnosis of primary sIgMD, the other immunodeficiencies and IgMD secondary to other diseases must be ruled out [9,10]. The pathogenesis of sIgMD is also unclear, although intrinsic IgM-secreting B-cell defects, lack of the helper function of $CD4^+$ cells, and excessive activity of $CD8^+$ suppressor cells have been hypothesized as the mechanisms [11].

The objective of this study was to analyze B-cell subsets in THI, UCH, partial IgAD, and sIgMD.

Material and Methods

Patient Characteristics

The study population comprised 41 patients with hypogammaglobulinemia (18 patients with THI and 23 patients with UCH), 16 with partial IgAD, and 16 with sIgMD who attended the Department of Pediatric Immunology-Allergy, Ankara University School of Medicine, Ankara, Turkey between January 2010 and April 2011, as well as 29 healthy controls. All patients were diagnosed according to the criteria of the European Society for Immunodeficiencies [1].

Definitions

As THI generally resolves at 3 years of age, we divided the hypogammaglobulinemia group into 2 groups to evaluate any differences between them.

The first group comprised patients with THI aged <3 years (n=18); the second group comprised patients with UCH aged ≥3 years (n=23). In both groups, patients had low serum IgG levels and/or IgA and IgM levels, normal specific vaccine antibody and isohemagglutinin titers, and no other causes of hypogammaglobulinemia or primary immunodeficiency.

Patients with partial IgAD were ≥4 years of age with IgA levels <2SD of the age-matched normal values. Patients with sIgMD had IgM levels <2SD of the age-matched normal values.

Peripheral blood lymphocyte subsets, absolute neutrophil and lymphocyte counts, antibody responses to vaccinations, and isohemagglutinin titers were all within the normal range. Ig levels were determined in order to rule out asymptomatic hypogammaglobulinemia. Children with acute infection, chronic diseases, or long-term usage of drugs were not included in the healthy control group.

In addition, we divided healthy controls into 3 groups to evaluate the variation of B-cell subsets with age. The results are given in Figure 1.

Serum Ig levels were measured using nephelometry. Normal values were interpreted according to age-matched healthy Turkish children, as reported by Tezcan et al [12]. Flow cytometric immunophenotyping (Cytomics FC 500 Flow Cytometer, Beckman Coulter Corp) was used to delineate distinct stages of peripheral B-cell maturation and differentiation.

B-cell subsets were analyzed according to the EUROclass classification system, which was developed for CVID patients, as follows [13]:

- Naive B cells ($CD19^+CD27^-IgD^+IgM^+$)
- Nonswitched memory (marginal zone) B cells ($IgM^+CD27^+IgD^+$)
- Switched memory B cells ($CD19^+CD27^+IgD^-IgM^+$)
- Activated B cells ($CD21^{low}CD38^{low}$)
- Transitional B cells ($CD38^{high}IgM^{high}$)

Blood (5 mL) was extracted from all patients for flow cytometry and to determine Ig levels. Whole blood samples (100 μL) were collected into tubes containing EDTA. Four-color immunophenotyping was carried out using the following fluorochrome-conjugated monoclonal antibodies: IgM PC5 (Beckman Coulter), IgD PE (BD Pharmingen, Clone IA6-2), CD27 FITC (BD Pharmingen, Clone M-T271), CD19 PC7 (Beckman Coulter, Clone J4.119), CD38 FITC (Beckman Coulter, Clone T16), and CD21 PE (Beckman Coulter, Clone BL13).

The gating strategies are shown in Figure 2, according to EUROclass.

The study was approved by the Ethics Committee of Ankara University School of Medicine.

All analyses were performed using SPSS 15.0 (SPSS Inc). A P value <.05 was considered to indicate statistical significance. The t test and mean values were used for normally distributed groups; the Mann-Whitney test and median values were used for nonnormally distributed groups.

Results

The THI group consisted of 18 patients with a mean age of 26 months (range, 18-36 months). Among these patients, low IgA levels were determined in 22.2%, low IgM levels in 5.5%, and low IgA and IgM levels in 27.7%. The UCH group consisted of 23 patients with a mean age of 6.7 years (range, 3-17 years).

Some of the patients were being followed before this study. Gender, age at diagnosis, and age at evaluation of the patients and gender and age of the healthy controls are summarized in Table 1. The differences in mean age and gender between patients and healthy controls were not statistically significant.

Total neutrophil and lymphocyte counts were normal in all patients and controls. Ig levels could not be compared, because the values were interpreted according to the specific age group.

Healthy controls were also divided into 2 subgroups by age for statistical analysis (≥3 years and <3 years). In the evaluation of B-cell subsets, nonswitched and switched memory cells did

Table 1. Patient Characteristics

Diagnosis, (n)	Age at Diagnosis, y Median (Range)	Age at evaluation, y Median (Min-Max)	Gender, No. (%)	
			Female	Male
Hypogammaglobulinemia (41)	2.1 (1.2-13)	3.5 (1.5-16)	16 (39)	25 (61)
THI (18)	1.7 (1.2-2)	2.2 (1.5-3)	5 (12)	13 (32)
UCH (23)	4.5 (1.5-11.5)	6.7 (3-17)	11 (26)	12 (30)
Partial IgA deficiency (16)	4.5 (1.4-11)	6.2 (4-16)	6 (38)	10 (62)
Selective IgM deficiency (16)	4.2 (0.5-11)	5.75 (1.1-13)	6 (38)	10 (62)
Healthy controls (29)		4 (1.5-16)	12 (41)	17 (59)

Abbreviations: Ig, immunoglobulin; THI, transient hypogammaglobulinemia; UCH, unclassified hypogammaglobulinemia.

Table 2. B-Cell Subtypes of Patients With Hypogammaglobulinemia and Healthy Controls

Diagnosis	Hypogammaglobulinemia group		Healthy Controls	
	THI (n=18)	Unclassified hypogammaglobulinemia (n=23)	<3 years (n=9)	≥3 years (n=20)
$CD19^+$ (Mean±SD)	16.1±6.0	13.3±5.2	16.7±3.5	13.3±5.6
		P=.031		*P*=.034
Naive $CD19^+CD27^-IgD^+$ (Mean±SD)	86.1±3.2	76±8.0	75.3±8.4	73.6±7.3
		P=.001	*P*=.001	
Nonswitched $IgM^+CD27^+IgD^+$ (Mean±SD)	7.5±2.7	8.2±2.7	9.0±2.0	7.9±2.2
Switched $CD19^+CD27^+IgD^-$ (Mean±SD)	40.3±15.4	45±17	45.2±16.4	41.7±11.4
Activated $CD21^{low}CD38^{low}CD27^+$ (Mean±SD)	4.1±1.6	5.7±1.7	7.6±5.6	6.4±2.3
		P=.014		
		P=.001		
Transitional $CD38^{high}$ IgM^{high} (Mean±SD)	8.4±5.0	7.9±2.4	8.3±2.8	7.4±3.5

not differ between the THI group, UCH group, and healthy controls. Naive B-cell percentages were found to be higher and activated B-cell values lower in the THI group than in the healthy controls (P=.001 and P=.001, respectively) and UCH group (P=.001 and P=.014, respectively). Total $CD19^+$ cell percentages were also significantly higher in patients and controls aged <3 years (P=.031 and P=.034, respectively) (Table 2).

Percentages of nonswitched memory B cells ($IgM^+CD27^+IgD^+$) were significantly reduced in patients with sIgMD (P=.028). Differences between B-cell subsets in patients with partial IgAD were not significant.

As expected, total B-cell and B-cell subset percentages other than nonswitched memory B cells decreased with age (Figure 1).

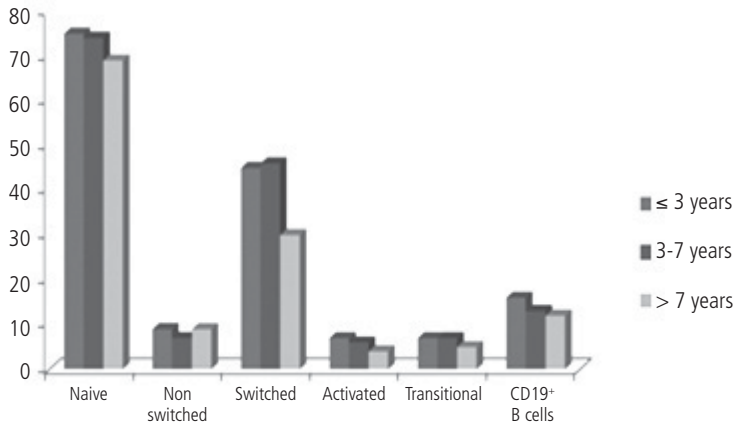

Figure 1. Distribution of B-cell subsets according to age.

Discussion

Diagnosis of the most common forms of primary immunodeficiency, such as IgAD, CVID, and THI is still based on clinical criteria and the exclusion of other specific diagnoses. While some genetic mutations in the B-cell signaling pathway have recently been defined in CVID patients in recent years, THI and IgAD are thought to be caused by delayed maturation of Ig isotypes [2,14,15]. Reduced memory B-cell levels have been reported in patients with THI and in patients with CVID [16-18].

CD27 with surface expression of IgD is used as a marker of human memory B-cells [18]. $CD27^+$ memory B cells can be subdivided into 2 distinct subsets: nonswitched cells (IgD^+CD27^+), which predominantly synthesize IgM, and switched cells (IgD^-CD27^+), which synthesize IgG, IgM, or IgA [19].

Several flow-cytometric approaches have been proposed to characterize B-cell subsets [13,20,21]. In the Bm1-Bm5 classification system defined by Piqueras et al [20], nonswitched and switched memory B cells could not be differentiated. We therefore decided to use the EUROclass classification, which is a combination of the Bm1-Bm5 system and the classification reported by Warnatz et al [21].

Low switched memory B-cell values have been reported in several immunodeficiencies, such as CVID [15,19,22,23], and subclassification of CVID patients according to the percentage of memory B cells has been shown to have clinical correlations: patients with decreased switched memory B-cell percentages had lower levels of IgG/IgM and higher rates of autoimmune diseases and bronchiectasis [15,23,24].

Age-dependent reference values for distinct B-cell populations have been reported [16,18,25]. Huck et al [16] reported a continuous increase with age in nonswitched and switched memory B cell values among total B cells in 4 different age groups of healthy controls. In our study, values of B-cell subsets other than nonswitched B cells tended to fall after 7 years of age. We considered that as age increased, so did exposure to environmental antigens, with the result that memory B-cell values increased and less mature B-cell values decreased. Other studies have shown that while the percentage of transitional and naive B cells decreased during the first 5 years of life, switched and nonswitched memory B-cell percentages increased slowly with age [18,19]. When our healthy controls were divided into 3 different age groups, the total percentage of B cells fell as expected after 3 years of age because of the decrease in naive B cells, which accounts for most of the B-cell population in young children.

In a recent analysis of B-cell subsets in 56 CVID, 37 THI, and 39 sIgAD patients, Bukowska-Strakova et al [17] showed that the percentage of switched memory B cells decreased in patients with THI in much the same way as in children with CVID. The authors suggested that patients with profoundly decreased switched memory B-cell values should be monitored for development of CVID. However, the same abnormalities in memory B cells were not observed in another group of THI patients [17], as was the case in our study. In contrast, nonswitched memory B-cell percentages were significantly lower in selective IgMD patients than in the healthy controls.

Moschese et al [26] determined the values of B-cell subsets in 32 patients with THI aged 12-36 months and suggested that lower levels of memory B cells in patients aged >2 years could be used to predict the persistence of hypogammaglobulinemia. In our study, we found no difference in memory B-cell percentages between patients with THI and UCH. In contrast, naive B-cell values were found to be significantly higher and activated B-cell values lower in the THI group than in the UCH group and healthy controls aged <3 years. These findings were interpreted as being due to defective differentiations from naive B cells to activated B cells. Patients in the UCH group were considered unlikely to improve with age, and the mechanism of hypogammaglobulinemia in this group seemed to be different from that in THI.

In the largest reported sIgMD series, Yel et al [27] defined the immunological and clinical features of 15 patients, although they did not analyze B-cell subsets. To date, B-cell subsets have been evaluated in only 1 patient with sIgMD [28]. In this patient, who presented with recurrent impetigo, switched memory B-cell percentages were profoundly low and T-cell receptor γ/δ values showed a large population of total lymphocytes. In our series (16 sIgMD patients), we found

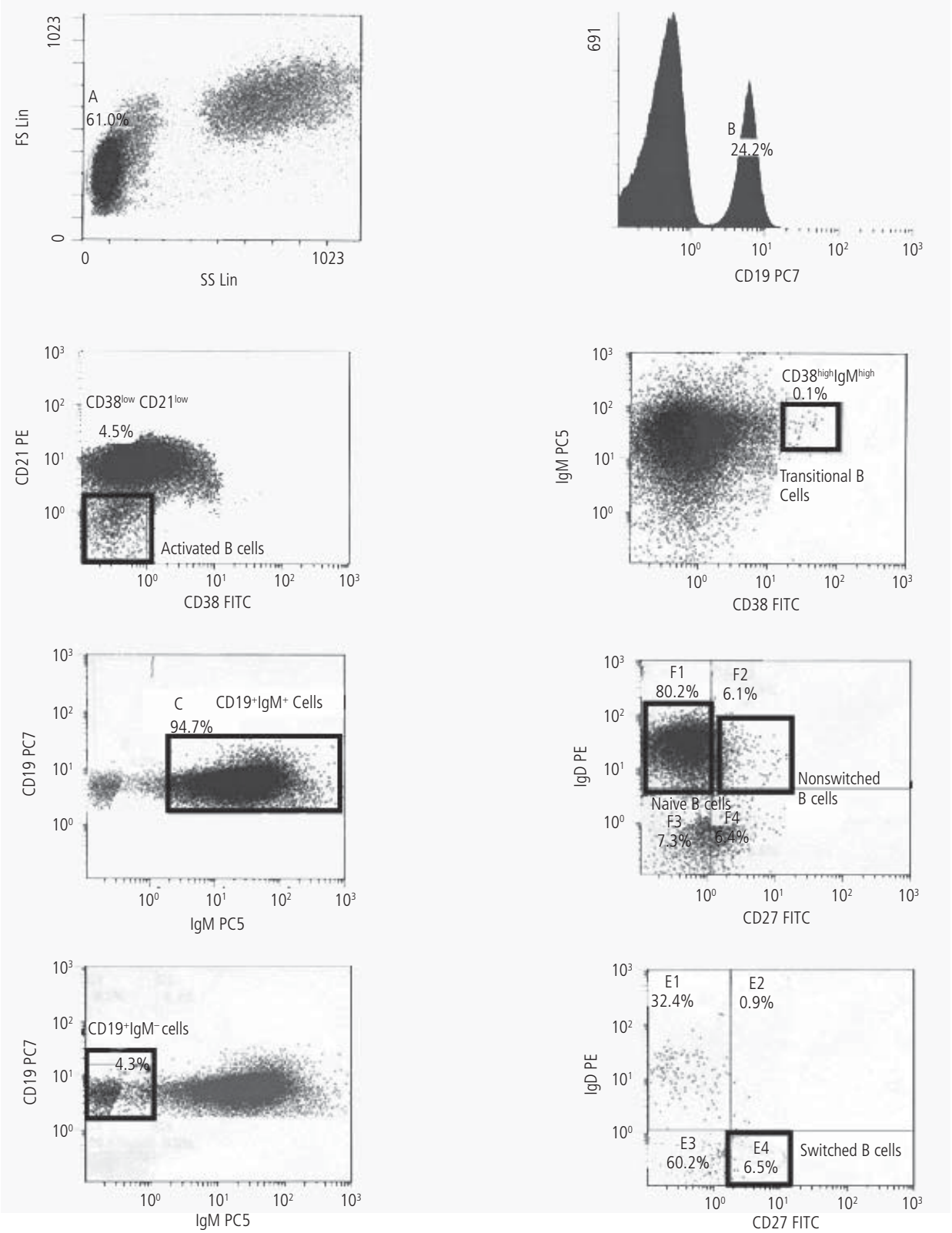

Figure 2. Immunophenotyping of B-cell differentiation stages. After gating on lymphocytes according to forward (FSC)/side scatter (SSC), B cells are characterized by CD19 staining. By staining for CD27 and IgD, naive $IgD^{+}IgM^{+}CD27^{-}$ B cells, $IgD^{+}IgM^{+}CD27^{+}$ nonswitched memory B cell and $IgD^{-}IgM^{-}CD27^{+}$ switched memory B cells were distinguished. CD21 and CD38 staining was performed to distinguish between $CD38^{low}CD21^{low}$ activated B cells and $CD38^{++}IgM^{high}$ transitional B cells.

significantly lower levels of nonswitched memory B cells, which were not present in the other disease groups. In contrast, Revy et al [29] reported a very high level of nonswitched memory B cells in a patient with autosomal recessive type 2 hyper IgM syndrome. In the light of these findings, we can speculate that low IgM levels are due to low percentages of nonswitched memory B cells. To our knowledge, the present study is the first report to describe low levels of nonswitched memory B-cell percentages in patients with sIgMD.

sIgAD is diagnosed in children after 4 years of age based on the diagnostic criteria of the European Society for Immunodeficiencies. Children <4 years with sIgAD should be followed up to evaluate persistence of disease beyond 4 years of age. As a result, only children >4 years were included in the partial sIgAD group of the present study. Low memory B-cell percentages were not observed in our patients with partial sIgAD, although they have been reported in sIgAD patients in a previous study [17], where it was thought that the mechanisms of selective and partial forms of IgAD might differ. We present the first analysis of B-cell subsets in partial sIgAD.

In conclusion, patients with symptomatic hypogammaglobulinemia should be followed regularly. It is expected that THI will resolve with maturation of the immune system and age. In our study, higher naive B-cell values in younger children than in healthy and older children with hypogammaglobulinemia support a B-cell maturation defect. In addition, we found low percentages for nonswitched memory B cells in patients with selective IgM deficiencies; this finding might explain the low IgM levels. These findings must be supported by further studies.

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Funda Erol Çipe

Ankara University School of Medicine
Department of Pediatric Immunology-Allergy
Ankara, Turkey
E-mail: ferol76tr@hotmail.com

